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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/916,780	07/27/2001	Yi Li	883933.0066	9604

21832 7590 10/01/2003

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EXAMINER

HELMER, GEORGIA L

ART UNIT	PAPER NUMBER
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1638

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DATE MAILED: 10/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/916,780

Applicant(s)

LI ET AL.

Examiner

Georgia L. Helmer

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 02 July 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-24 is/are pending in the application.
- 4a) Of the above claim(s) 7-22 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-6 and 23 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: |

DETAILED ACTION

Status of the Claims

1. The Office acknowledges receipt of Applicants Response; dated 2 July 2003, paper number 14.
2. Applicant has amend claim 1. New claims 23 and 24 have been added. Applicant should make note that new added claims with this amendment need to be number sequentially from the last claim, so that what Applicant had labeled new claims 7 and 8, are renumbered claims 23 and 24.
3. This action is made FINAL necessitated by Applicant's amendment.
4. All rejections not addressed below have been withdrawn.
5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claims 1-6 are examined in the instant application.
6. This application contains claims 7-22, drawn to an invention nonelected with traverse in Paper No. 11. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections - 35 USC § 112, second paragraph

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7. Claims 1-6 and 23-24 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for reasons of record. To the extent that this is a new rejection it is necessitated by Applicant's amendment.

In claim 1. "Transiently transgenic plant" is unclear because it describes a plant which is transgenic initially and then become non-transgenic.

Applicant traverses, stating primarily (response, p3) that the invention teaches the production of a plant that is transgenic (i.e. comprises a heterologous gene functionally coding for a desired phenotypic trait), but is only transiently transgenic in that the nucleic acid comprising the heterologous gene is excised from the genome of the plant at the time and under certain conditions. Applicant further asserts that the plant that was rendered transgenic by transformation with nucleic acid comprising the gene of interest is no longer transgenic, i.e. the plant is transiently transgenic as the genome of the plant no longer contains the heterologous nucleic acid comprising the gene of interest. That this resulting plant is indistinguishable from the wild-type genome.

Applicant's traversal has been considered and is unpersuasive . "Transiently transgenic plant" is unclear because it describes a plant which is transgenic initially and then become non-transgenic, as stated for reasons of record. The instant invention is to a transgenic plant which transiently expresses a trait, and then excises the nucleic acid of the gene of interest. This is *not a transiently transgenic plant*—the remaining plant is not wild-type, rather the remaining plant contains other transgenic DNA , such as the

recombinase gene. Thus, this is a transgenic plant both before and after the excision of the gene of interest.

Claim 1 is further unclear because the claim recites a number of DNA sequences which comprise the cassette, but gives no order of the sequences with respect to one another, and with the exception of the promoter of 1 a (iv), does not describe operable relationships of the various DNA sequences.

Applicant has amended claim 1 to recite (v) "the DNA sequence expressing the recombinase type protein is located in a 5' and /or 3' position to the excision sequence which flank the heterologous DNA".

Applicant's traversal has been considered and is unpersuasive This rejection is maintained for reasons of record. The "5' and /or 3' position" language only says that the recombinase DNA sequence is not inside the body of any given excision sequence—it gives no further functional linkage than this. What is the relationship of the excision sequences to the heterologous DNA? Where is the gene of interest? Where is the recombinase? What is missing here is a working description of the proposed claimed cassette.

Claim Rejections - 35 USC § 112-new matter

8. Claims 23 and 24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejected subject matter is the

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recombinase type proteins consisting of the grouping in claim 23, and the promoter gene sequence selected from the group consisting of the grouping of claim 24.

Applicant is invited to point out the pages and line numbers in the specification where the recombinase type proteins consisting of the grouping in claim 23, and the promoter gene sequence selected from the group consisting of the grouping of claim 24 can be found. Absent such support, Applicant is required to cancel the new matter in response to this Office Action.

Claim Rejections - 35 USC § 112-enablement

9. Claims 1-6 main rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The rejection is restated below.

Enablement is considered in view of the *Wands* factors (MPEP 2164.01(a)):

Nature of the invention. Applicant's claims are drawn to a method of producing a transgenic plant which temporarily convey a phenotypic trait to a plant, comprising constructing a gene cassette comprising a DNA sequence conferring a trait, one or more DNA sequences expressing a recombinase-type protein, at least one pair of DNA excision sequences flanking the heterologous DNA and a transiently active promoter operably linked to the DNA sequence expressing the recombinase -type protein such that when the promoter is activated, the recombinase is expressed; introducing the cassette into a plant and expressing the DNA sequences with the cassette to a stimulus

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that activates the promoter and the recombinase excises the heterologous DNA from the plant genome. Claims are also drawn to gene cassettes comprising a marker gene, transiently active promoters active only in certain organs of the plant, or only at specific stages in the plant's development, or responsive to external stimuli, and to external stimuli comprising chemicals, heat shock, electromagnetic radiation, and exposure to reduced temperatures. The claimed methods use recombinase-type systems to modify gene expression.

State of the prior art. The art is such that the skilled person can introduce genes into plant cells but that generation of a given particular phenotype is unpredictable. Gene expression levels and inheritance are unpredictable (Deroles, SC and Gardner, RC; (1998) Plant Molecular Biology 11: 355-364; Dunwell, JM and Paul, EM (1990) Outlook on Agriculture 19, 103-109; Finnegan J and McElroy D (1994) Bio/Technology 12: 883-888). Organ-specific gene expression in plants is variable (Van-der-Hoeven C et. al. (1994) Transgenic Research 3: 159-166). Recombinase mediated excision of appropriately flanked DNA sequences is variable and yields chimeric phenotypes having both recombined and unrecombined DNA (Gidoni, D. et al, Supplement to Plant Molecular Biology Reporter 18:2, S 03-40; ISPMB abstracts, June 18-24, 2000). Recent studies (Gidoni, D et al (2001) Euphytica 121: 145-156) of embryonal recombination and germline inheritance of recombined tobacco loci show variable recombination efficiencies (Godini 2001, 146 and 152). The claimed methods require use of recombinase-type systems to delete appropriately flanked DNA sequences.

Breadth of the claims. Claims are broadly drawn to any recombinase, any plant, any trait and any marker gene. Recombinases and recombinase sites are encompassed broadly; Applicant describes site specific recombinases, but claims all recombinases.

Working examples. There are no working examples.

Guidance in the specification. The specification contains three prophetic examples: Prophetic Example 1 describes (p 32) a gene cassette for the reversible introduction of heterologous DNA sequences into a genome of a vegetatively propagated plant. Prophetic Example 2 describes (p 33) a second gene cassette for the reversible introduction of heterologous DNA sequences into a genome of a vegetatively propagated plant. And Prophetic Example 3 (p 35) describes a gene cassette for the reversible introduction of heterologous DNA sequences into a genome of a sexually propagated plant.

Applicant describes a series of steps that one of skill in the art could take to try to produce various desired outcomes. These desired outcomes are all predicated on the ability of a recombinase gene being expressed and successfully excising a DNA specific sequence from a DNA sequence flanked by DNA recombinase excision sequences. If the DNA excision reactions do not function faithfully and at a very high frequency, none of the more complicated steps of the multi-tiered cascade, will function as desired. Applicant gives no specific details of any DNA constructs, nor any results of use of the various generally described systems to function as desired. Various parameters that need to be defined, such as: what DNA sequence do you put where, in

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what proximity to other DNA sequences, in what orientation with respect to transcription, in cis or trans configuration to one another, and how large a DNA sequence will function in the various pieces. Applicant offers no information on any of this, other than to list various pieces of DNA which might work in the various desired functions.

Predictability of the art. The physiological art in general is acknowledged to be unpredictable (MPEP 2164.03). Above discussions of the state of the art are repeated below:

The art is such that the skilled person can introduce genes into plant cells but that generation of a given particular phenotype is unpredictable. Gene expression levels and inheritance are unpredictable (Deroles, SC and Gardner, RC; (1998) Plant Molecular Biology 11: 355-364 ; Dunwell, JM and Paul, EM (1990) Outlook on Agriculture 19, 103-109 ; Finnegan J and McElroy D (1994) Bio/Technology 12: 883-888). Organ-specific gene expression in plants is variable (Van-der-Hoeven C et. al. (1994) Transgenic Research 3: 159-166). Recombinase mediated excision of appropriately flanked DNA sequences is variable and yields chimeric phenotypes having both recombined and unrecombined DNA (Gidoni, D. et al, Supplement to Plant Molecular Biology Reporter 18:2, S 03-40; ISPMB abstracts, June 18-24, 2000). Recent studies (Gidoni, D et al (2001) Euphytica 121: 145-156) of embryonal recombination and germline inheritance of recombined tobacco loci show variable recombination efficiencies (Godini 2001, 146 and 152).

Amount of Experimentation necessary. Applicant has provided no guidance on how to predictably eliminate inoperable embodiments from a virtually ad infinitum of

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possibilities other than by random trial and error, which is excessive experimentation and an undue burden.

Specifically, for any given set of transgenes in a plant, what phenotype is the desired one? For any given set of transgenes, criteria for parameters such as copy number, expression level (RNA or protein) of selectable marker, expression level (or lack of expression) of genes of interest, expression patterns (or lack of expression) of genes of interest, and stability of transgenes through generations, need to be defined. The enablement of creation of a transiently transgenic plant would require an infinite number of variables to be defined and optimized.

In view of the breadth of the claims (to any recombinase, any plant, any trait and any marker gene), the lack of guidance in the specification, and the unpredictability in the recombinase art, undue trial and error experimentations would be required to enable the invention as commensurate in scope with the claims.

These questions remain unanswered by Applicant. This rejection is maintained.

Applicant traverses, stating primarily that their references are not current and do not apply to the excision of transgenes in a parent plant.

Applicant's traversal has been considered and is unpersuasive because these references still apply and the unpredictability remains. Applicant uses the same methods for transformation as those described in the references cited. And Applicant's methods for excision of transgenes require expression of transgenes.

Applicant traverses, stating primarily that the claims have been amended.

Applicant's traversal has been considered and is unpersuasive because the claims still encompass subject matter that is not enabled.

Applicant traverses, stating primarily that no working example is required.

Applicant's traversal has been considered and is unpersuasive because working examples are required when the art is unpredictable, in addition to the other Wands factors. As stated in the last Office Action, it would require undue experimentation to make and use this invention.

Claim Rejections - 35 USC § 102

10. Claims 1-6 remain rejected under 35 U.S.C. 102(b) as being anticipated by Oliver et al, US 5,723,765, issued March 3, 1998.

Oliver teaches a method comprising constructing a gene cassette comprising a DNA sequence conferring a phenotypic trait, (col 35, lines 33-34), 13-17), a DNA sequence expressing a recombinase-type protein (col 35, lines 22-24), at least one pair of DNA excision sequences cleavable by the recombinase type proteins wherein the excision sequences flank heterologous DNA (col 35, lines 18-20), and a transiently activated promoter operably linked to the DNA sequence expressing the recombinase (col 35, lines 33-34), introducing the cassette into the plant genome (col 35, line 11), and exposing the DNA sequences with the cassette to a stimulus that activates the promoter, expressing the recombinase, and excises the DNA from the genome of the plant (col 42, lines 26-33). Oliver further teaches a marker gene (col 12, line 4), organ specific promoters (col 6, lines 5-16), development stage specific promoters (col 5, lines

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65-67), and promoters activated in response to external stimuli, including exposure to a specific chemical species (col 5, lines 38-45).

Accordingly, Oliver anticipates the claimed invention.

Applicant traverses, stating primarily (p. 8) that Oliver does not suggest or teach that it is possible, after expression of the transgene, to return the plant to its wild-type state.

Applicant's traversal has been considered and is unpersuasive because Applicant does not suggest or teach that it is possible, after expression of the transgene, to return the plant to its wild-type, for all the reasons record recited above. Furthermore, the evidence for nonobviousness should be commensurate with the scope of the claims.

Remarks

11. No claim is allowed.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

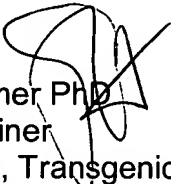
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the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Georgia L. Helmer whose telephone number is 703-308-7023. The examiner can normally be reached on 8:30 - 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on 703-306-3218. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.


Georgia Helmer PhD
Patent Examiner
Art Unit 1638, Transgenic Plants
September 30, 2003


ELIZABETH F. McELWAIN
PRIMARY EXAMINER
GROUP 1600